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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	10

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/554,267	Applicant(s) PEYMAN ET AL	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6
18)☐ Interview Summary (PTO-413) Paper No(s) _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other

DETAILED ACTION

Claims 24-44 are pending in the instant application.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Information Disclosure Statement

Reference No. 1 of the IDS filed May 12, 2000, Paper No. 6, has not been considered because no translation has been provided.

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the revised guidelines for written description, revised December, 1999 and January, 2000. The claims are drawn to oligonucleotides which bind to and inhibit the expression of any and/or all isoforms of tenascin. A subset of the claims is drawn such oligonucleotides which further comprise modifications (i.e. claim 27), and another subset of the claims is drawn to any and/or all derivatives of oligonucleotides conjugated to a 2'5'-bonded oligoadenylate (i.e. claim 28). Additionally, a different subset of the claims includes the term "placenta extracts" (i.e. claims 39 and 40). The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genera comprising any and/or all isoforms of tenascin and further comprising any and/or all oligonucleotide modifications, nor of derivatives of oligonucleotides conjugated to a 2'5'-bonded oligoadenylate or placenta extracts. The scope of the claims includes numerous structural variants in each of the genera, and the genera are highly variant because a significant number of structural variants between genus members is permitted. Concise structural features that could distinguish compounds in the genera from others are missing from the disclosure and the claims. Since the disclosure fails to describe the common attributes or characteristics concisely identifying members of the proposed genera, and because each genus is highly variant, the description

provided for defining members of the genera is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genera claimed. Thus, Applicants were not in possession of the claimed genera.

Claims 24-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the synthesis and characterization of the antisense oligonucleotide comprising SEQ ID NO: 24 which further comprises modified internucleoside linkages, does not reasonably provide enablement for compositions, kits and methods for the targeting and/or inhibition of expression of any and/or all isoforms of tenascin in vivo and in vitro comprising the administration of antisense oligonucleotides which target nucleic acids encoding any and/or all isoforms of tenascin, as well as for treatment effects provided comprising the administration of said antisense, and which antisense oligonucleotides may further include any and/or all modifications, and any and/or all derivatives of oligonucleotides conjugated to a 2'5'-bonded oligoadenylate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. .

The claims are drawn to compositions, kits and methods for the targeting and/or inhibition of expression of any and/or all isoforms of tenascin in vivo and in vitro comprising the administration of antisense which target nucleic acids encoding any and/or all isoforms of tenascin, as well as for treatment effects provided comprising the administration of said antisense, and which antisense oligonucleotides may further include any and/or all modifications,

and any and/or all derivatives of oligonucleotides conjugated to a 2'5'-bonded oligoadenylate. The claims are also drawn to diagnostic or test kits comprising oligonucleotides which target tenascin.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed. This determination is based on several factors which, when considered together, illustrate that the art of gene delivery, expression and/or inhibition is in its infancy and highly unpredictable. The discussion is also based on references whose teachings show that, despite a tremendous amount of experimentation by highly skilled artisans in the field of gene delivery and expression in vivo, there remain significant hurdles known in the art to make and/or use the invention over the scope claimed.

The nature of the invention. Methods of targeting nucleic acids into host cell in vivo fall into the broad area known as gene therapy methods. While delivery of nucleic acids in and of itself is not considered as therapy per se, in vivo delivery shares many of the obstacles recognized for the actual therapy methods because successful therapy methods are for the most part based on the ability to deliver, functionally and appropriately express exogenous nucleic acids to cells or tissues of interest.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene delivery. Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids (such as

antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating a disease state was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and for a given target cell (See entire article, especially page 4, section 2.)

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting any and/or all isoforms of tenascin in vitro or in vivo, nor of providing any treatment for any conditions in an organism, which treatments or inhibition comprise the administration of oligonucleotides which target nucleic acids encoding any and/or all isoforms of tenascin, either alone or in combination with the administration of photochemotherapy, placenta extracts or cultured melanocytes. Applicants have not provided guidance in the specification toward a method of providing any diagnoses or diagnostic tests using the oligonucleotides of the claimed invention. The specification teaches the design of

oligonucleotides which target nucleic acids encoding one isoform of tenascin, which oligonucleotides also include modified internucleotide linkages and modified sugar and nucleobase residues. The specification also teaches the synthesis and characterization of SEQ ID NO: 24 with such modifications and a pharamaceutical preparation further comprising Dermatop^{R}. The specification fails to teach the successful delivery of any antisense oligonucleotides and subsequent inhibition of the appropriate target gene in a whole organism whereby any and/or all isoforms of tenascin expression are inhibited, and further whereby treatment effects are provided for any conditions in any organism. The specification fails to teach the diagnoses or diagnostic testing of anything using the antisense oligonucleotides which target a particular isoform of tenascin. One skilled in the art would not accept on its face the examples given in the specification of the design, synthesis or characterization of SEQ ID NO: 24 as being correlative or representative of the diagnoses or testing of any condition, nor of the administration of antisense in any and/or all organisms such that any and/or all isoforms of tenascin are appropriately inhibited and further where treatment effects for any condition are provided in view of the lack of guidance in the specification and known unpredictability associated with the administration and in vivo delivery of antisense which target any and/or all isoforms of tenascin, which antisense oligonucleotides may further include any and/or all modifications, and any and/or all derivatives of oligonucleotides conjugated to a 2'5'-bonded oligoadenylate, and further regarding the subsequent treatment of any conditions in any organism using such compositions. The specification as filed fails to provide any particular guidance

which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by antisense administered, and specifically regarding the instant target gene tenascin and all of its isoforms.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods for the inhibition of expression of any and/or all isoforms of tenascin in vivo and in vitro comprising the administration of antisense which target nucleic acids encoding any and/or all isoforms of tenascin, as well as for treatment effects provided comprising the administration of said antisense, which antisense oligonucleotides may further include any and/or all modifications, and any and/or all derivatives of oligonucleotides conjugated to a 2'5'-bonded oligoadenylate. The claims are also drawn to diagnostic or test kits comprising these antisense oligonucleotides which target any and/or all isoforms of tenascin. In order to practice the invention claimed, it would require undue trial and error and undue experimentation beyond which is taught in the specification to practice the invention drawn to any route of administration of antisense oligonucleotides to an organism such that the target genes comprising any and/or all isoforms of tenascin are appropriately and specifically inhibited, and further whereby treatment for such conditions as vitiligo as well as any and/or all hypopigmentation disorders, psoriasis, cancers, inflammatory disorders and cardiovascular disorders is provided. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate

cell and /or tissues harboring the target genes such that the expression of any and/or all isoforms of tenascin are inhibited in vivo, and further whereby treatment effects for vitiligo, any and/or all hypopigmentation disorders, psoriasis, cancers, inflammatory disorders and cardiovascular disorders are provided. Furthermore, the *de novo* determination of the successful diagnoses for relevant conditions (?) comprising the antisense oligonucleotides of the instant invention must also be provided. Since the specification fails to provide any particular guidance for the diagnoses of anything using said antisense oligonucleotides, and fails to provide any particular guidance for the successful delivery of antisense oligonucleotides targeting any and/or all isoforms of tenascin in any organism, and further whereby their expression is inhibited appropriately and treatment effects are provided for vitiligo, and for any and/or all hypopigmentation disorders, psoriasis, cancers, inflammatory disorders and cardiovascular disorders, and since determination of these factors for a particular antisense oligonucleotide, including antisense oligonucleotides comprising any and/or all modifications, and any and/or all derivatives of oligonucleotides conjugated to a 2'5'-bonded oligoadenylate, in a particular organism with a particular condition is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans et al.

Evans et al teach an oligonucleotide comprising between 7-17 oligonucleotides which targets a part of a tenascin gene and inhibits its expression, which oligonucleotide is combined with physiologically tolerable salts (See SEQ ID NO: 4 of Evans et al and the accompanying alignment data to SEQ ID NO: 18 of the instant application).

Claims 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Sommergruber et al.

Sommergruber et al teach an oligonucleotide comprising 7-17 oligonucleotides which targets a part of a tenascin gene and inhibits its expression, which oligonucleotide is combined with physiologically tolerable salts (See SEQ ID NO: 14 of Evans et al and the accompanying alignment data to SEQ ID NO: 18 of the instant application).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-35 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Denner et al, Cleek and Cleek et al in view of Baracchini et al and Friesen et al insofar as the claims are drawn to antisense oligonucleotides between 7 and 17 oligonucleotides in length which target nucleic acids encoding tenascin and inhibit its expression in vitro, and which oligonucleotides optionally comprise modified internucleotide linkages, modified sugar and nucleobase residues, 3'-3' or 5'-5' inversions, or conjugation of the oligonucleotide to a polylysine, lipid steroid or lipophilic molecules.

Denner et al, Cleek and Cleek et al all teach antisense oligonucleotides which target and inhibit the expression in vitro of known tenascin isoforms, which antisense oligonucleotides optionally include internucleotide linkage modifications such as phosphorothioates or morpholidates, and their conjugation to lipids, and which oligonucleotides are prepared on solid phase, and which oligonucleotides are administered to cells in vitro in physiologically tolerable salts, whereby such antisense target the 5' and 3' untranslated and the coding regions of tenascin

(See entire documents, especially: Denner et al at Table 1 of page 31 and pages 13-18; Cleek et al at page 526, last paragraph on the right and Figure 1 on page 527).

The primary references do not teach antisense oligonucleotides between 7 and 17 nucleotides in length and including SEQ ID Nos: 2-20, which target and inhibit tenascin expression, nor do they teach all of the nuclebase and sugar modifications set forth in the claims including 3'-3' or 5'-5' inversions.

Baracchini et al teach the incorporation of various modifications into antisense oligonucleotides for enhancing cellular uptake, target binding and stability, including an array of sugar, nucleobase and internucleoside modifications and the conjugation of antisense to various effector molecules. Baracchini et al also teach antisense oligonucleotides comprising lengths between 8 and 30 nucleotides (See entire text, especially column 6 through column 8; claims 1 and 6-10).

Friesen et al teach the incorporation of 3'-3' and 5'-5' inversions into oligonucleotides for increasing their stability (See especially column 3, lines 19-40).

It would have been obvious to one of ordinary skill in the art to design and utilize oligonucleotide antisense molecules which target and inhibit the expression of tenascin because the nucleic sequences encoding this particular isoform of tenascin have been taught previously by Denner et al and furthermore Denner et al, Cleek and Cleek et al all teach the inhibition of tenascin expression in vitro using antisense. One of ordinary skill in the art would have been motivated to inhibit the expression of various isoforms of tenascin because the expression of

various forms of tenascin has been found associated with various conditions including proliferative diseases such as cancers as taught previously by Cleek et al and Denner et al. One of ordinary skill in the art would have been motivated to incorporate nucleobase, sugar and internucleotide linkage modifications into antisense oligonucleotides because such modifications have been shown to increase stability of antisense from nuclease degradation, or to enhance cellular uptake and target binding, as taught previously by Denner et al, Baracchini et al and Friesen. One of ordinary skill in the art would have expected the claimed sequences of the instant application to inhibit the expression of tenascin in vitro because very similar sequences as those disclosed in the instant application had been taught previously by Denner et al, including slightly larger oligonucleotides which include the oligonucleotide sequences claimed. Furthermore Baracchini et al teach a suitable range for antisense oligonucleotide length to comprise between 8 and 30 nucleotides, whereby oligonucleotides with lengths shorter than 17 nucleotides are routinely used in the field of antisense for targeting and inhibiting the expression of target genes in vitro.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ANDREW WANG
PATENT EXAMINER
TC 1600

JZ

April 5, 2001